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Appl. No. 10/579,230
Atty. Ref.: 620-439
Amendment After Final Rejection
November 5, 2010

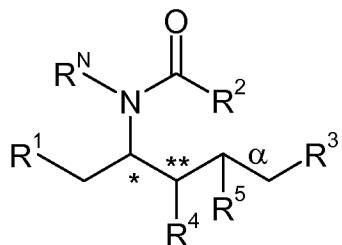
AMENDMENTS TO THE CLAIMS:

Please amend the claims as follows:

Claims 1-91. (Canceled)

92. (Currently Amended) A pharmaceutical formulation suitable for parenteral administration comprising:

- (i) an amphiphilic drug selected from the group consisting of an anthracycline and an alkaloid; and
- (ii) a short-chain sphingolipid selected from compounds of the following formula:



wherein:

R¹ is independently:

- an O-linked saccharide group; or
- an O-linked polyhydric alcohol group;

or:

R¹ is independently:

- an O-linked (optionally N-(C₁₋₄alkyl)-substituted amino)-C₁₋₆alkyl-phosphate group; or

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an O-linked (polyhydric alcohol-substituted)-C₁₋₆alkyl-

phosphate group;

R² is independently C₃₋₉alkyl,

and is independently unsubstituted or substituted;

R³ is independently C₇₋₁₉alkyl,

and is independently unsubstituted or substituted;

R⁴ is independently -H, -OH, or -O-C₁₋₄alkyl;

R^N is independently -H or C₁₋₄alkyl;

the bond marked with an alpha (α) is independently a single bond or a double bond;

if the bond marked with an alpha (α) is a double bond, then R⁵ is -H;

if the bond marked with an alpha (α) is a single bond, then R⁵ is -H or -OH;

the carbon atom marked (*) is independently in an R-configuration or an

S-configuration;

the carbon atom marked (**) is independently in an R-configuration or an S-configuration;

with the proviso that when R¹ is an O-linked saccharide group which is derived from galactopyranose, then R¹ is D-galactopyranosyl-β1-;

and pharmaceutically acceptable salts thereof.

Claim 93. (Canceled)

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94. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein said drug is an anthracycline.

95. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein said drug is selected from: doxorubicin, idarubicin, epirubicin, aclarubicin, mitozantrone, and daunorubicin, and salts thereof.

96. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein said drug is doxorubicin or doxorubicin hydrochloride.

97. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein said drug is an alkaloid.

98. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein said drug is selected from: topotecan and camptothecin.

99. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R² is linear.

100. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R² is linear; and has from 0 to 3 carbon-carbon double bonds.

101. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R² is unsubstituted or substituted with from 1 to 3 substituents selected from C₁₋₄alkyl, -OH, C₁₋₄alkoxy, -C(=O)OH, and -C(=O)O-C₁₋₄alkyl.

102. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R² is -(CH₂)_nCH₃, wherein n is an integer from 4 to 8.

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103. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R² is -(CH₂)_nCH₃, wherein n is an integer from 6 to 8.

104. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R² is -(CH₂)₆CH₃.

105. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein the bond marked alpha is a double bond and R⁵ is -H.

106. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein the bond marked alpha is a single bond; and R⁵ is -H.

107. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein the bond marked alpha is a single bond; and R⁵ is -OH.

108. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R³ is linear.

109. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R³ is linear; and has from 0 to 3 carbon-carbon double bonds.

110. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R³ is unsubstituted or substituted with from 1 to 3 substituents selected from C₁-4alkyl, -OH, C₁-4alkoxy.

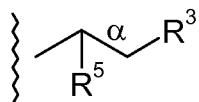
111. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R³ is -(CH₂)_nCH₃, wherein n is an integer from 8 to 16.

112. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R³ is -(CH₂)₁₂CH₃.

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113. (Previously Presented) A pharmaceutical formulation according to claim 92,

wherein the moiety:



is selected from the following:

- (CH₂)₈-CH₃;
- (CH₂)₁₀-CH₃;
- (CH₂)₁₂-CH₃;
- (CH₂)₁₄-CH₃;
- (CH₂)₇-CH=CH-(CH₂)₅-CH₃;
- (CH₂)₁₆-CH₃;
- (CH₂)₇-CH=CH-(CH₂)₇-CH₃;
- (CH₂)₉-CH=CH-(CH₂)₅-CH₃;
- (CH₂)₇-[CH=CH-CH₂]₂-(CH₂)₃-CH₃;
- (CH₂)₇-[CH=CH-CH₂]₃-CH₃;
- (CH₂)₄-[CH=CH-CH₂]₃-(CH₂)₃-CH₃;
- (CH₂)₇-[CH=CH]₃-(CH₂)₃-CH₃;
- (CH₂)₁₈-CH₃;
- (CH₂)₆-[CH=CH-CH₂]₂-(CH₂)₆-CH₃;
- (CH₂)₃-[CH=CH-CH₂]₃-(CH₂)₆-CH₃;
- (CH₂)₃-[CH=CH-CH₂]₄-(CH₂)₃-CH₃;

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$-(\text{CH}_2)_{20}-\text{CH}_3;$

analogs of the foregoing wherein the left-most $-(\text{CH}_2)_2-$ is replaced with $-\text{CH}=\text{CH}-$; and

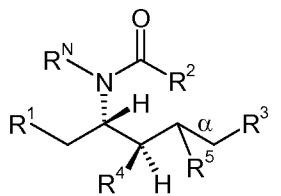
analogs of the foregoing wherein the left-most $-(\text{CH}_2)-$ is replaced with $-\text{CH}(\text{OH})-$.

114. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R^4 is $-\text{H}$, $-\text{OH}$, $-\text{OMe}$, $-\text{OEt}$, $-\text{O}(\text{iPr})$, $-\text{O}(\text{nPr})$, $-\text{O}(\text{nBu})$, $-\text{O}(\text{iBu})$, $-\text{O}(\text{sBu})$, or $-\text{O}(\text{tBu})$.

115. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R^4 is $-\text{OH}$.

116. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R^N is $-\text{H}$, $-\text{Me}$, or $-\text{Et}$.

117. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein the carbon atoms marked (*) and (**) have a configuration as shown in the following formula:



118. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R^1 is an O-linked saccharide group.

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119. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R¹ is an O-linked mono-, di-, or tri-saccharide group.

120. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R¹ is comprises a group or groups selected from:

arabinose, lyxose, ribose, xylose,
allose, altrose, glucose, mannose, gulose, idose, galactose, and
talose;
and derivatives thereof.

121. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R¹ is an O-linked mono-, di-, or tri-saccharide group comprising a group or groups selected from:

arabinose, lyxose, ribose, xylose,
allose, altrose, glucose, mannose, gulose, idose, galactose, talose,
sucrose, maltose, lactose, cellobiose, galabiose,
globotriaose, isoglobotriaose, mucotriaose, lactotriaose,
neolactotriaose gangliotriaose, galatriose, mollutriose, and antotriose;
and derivatives thereof.

122. (Previously Presented) A pharmaceutical formulation according to claim 120, wherein said saccharide group derivatives are selected from deoxy, di-deoxy, di-deoxy-di-dehydro, methoxy, acetoxy, carboxylic acid, sulfuric acid, amino-deoxy, N-acetyl-amino-deoxy, or N-sulfo-amino-deoxy.

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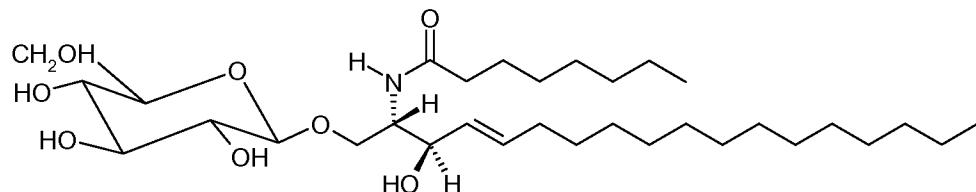
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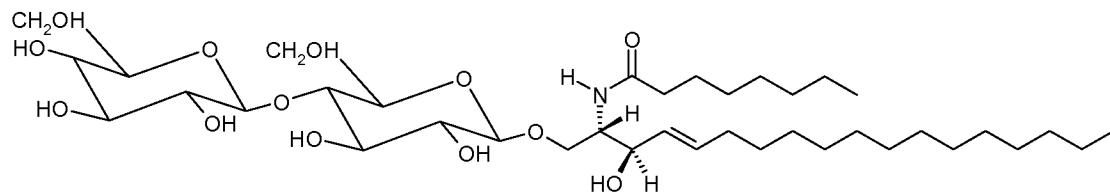
123. (Previously Presented) A pharmaceutical formulation according to claim 92,

wherein said short-chain sphingolipid has the following formula (C₈-GlcCer):



124. (Previously Presented) A pharmaceutical formulation according to claim 92,

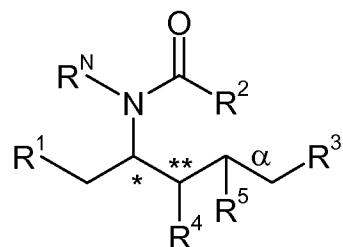
wherein said short-chain sphingolipid has the following formula:



125. (Previously Presented) A pharmaceutical formulation comprising:

(i) a drug; and

(ii) a short-chain sphingolipids selected from compounds of the following formula



wherein:

R¹ is independently an O-linked polyhydric alcohol group

R² is independently C₃₋₉alkyl,

and is independently unsubstituted or substituted;

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R³ is independently C₇₋₁₉alkyl,

and is independently unsubstituted or substituted;

R⁴ is independently -H, -OH, or -O-C₁₋₄alkyl;

R^N is independently -H or C₁₋₄alkyl;

the bond marked with an alpha (α) is independently a

single bond or a double bond;

if the bond marked with an alpha (α) is a double bond, then R⁵ is -H;

if the bond marked with an alpha (α) is a single bond, then R⁵ is -H or -OH;

the carbon atom marked (*) is independently in an R-configuration or an

S-configuration;

the carbon atom marked (**) is independently in an R-configuration or an

S-configuration;

and pharmaceutically acceptable salts thereof.

126. (Previously Presented) A pharmaceutical formulation according to claim 125, wherein R¹ comprises a group selected from: ethanediol (glycol), propanediol, butanediol, glycerol, and erythritol.

127. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein R¹ is:

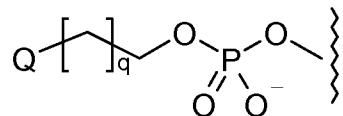
an O-linked (optionally N-(C₁₋₄alkyl)-substituted amino)-C₁₋₆alkyl-phosphate group; or

an O-linked (polyhydric alcohol-substituted)-C₁₋₆alkyl-phosphate group.

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128. (Previously Presented) A pharmaceutical formulation according to claim 92,

wherein R¹ is:



wherein:

q is an integer from 0 to 5;

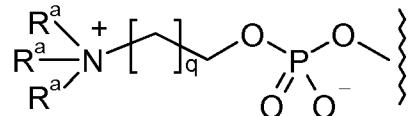
Q is: -NH₂, -NHR^a, -NR^a₂, or -NR^a₃⁺; or:

Q is a polyhydric alcohol group, linked via an oxygen atom;

each R^a is linear or branched saturated C₁₋₄alkyl.

129. (Previously Presented) A pharmaceutical formulation according to claim 92,

wherein R¹ is:



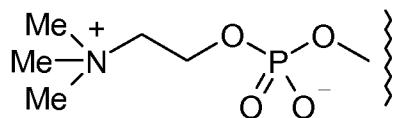
wherein:

q is an integer from 0 to 5; and

each R^a is a C₁₋₄alkyl group.

130. (Previously Presented) A pharmaceutical formulation according to claim 92,

wherein R¹ is:



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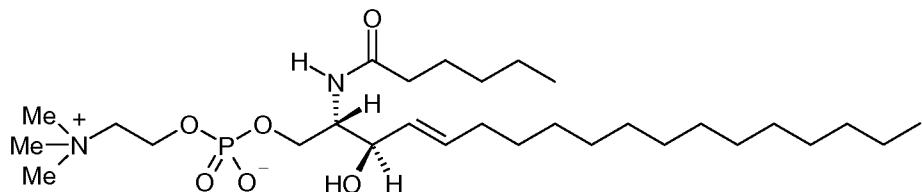
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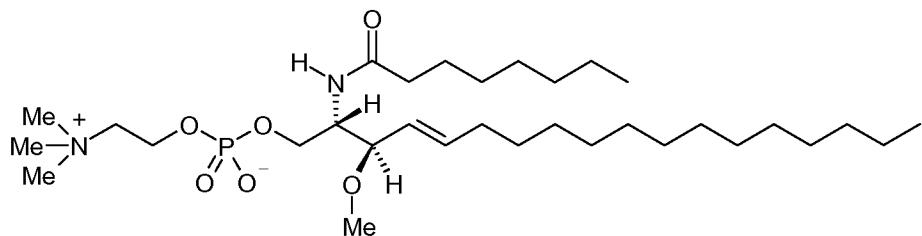
131. (Previously Presented) A pharmaceutical formulation according to claim 92,

wherein said short-chain sphingolipid has the following formula ("C₆-SM"):



132. (Previously Presented) A pharmaceutical formulation according to claim 92,

wherein said short-chain sphingolipid has the following formula ("3-O-methyl-C₈-SM"):



133. (Previously Presented) A pharmaceutical formulation according to claim 128, wherein Q is a polyhydric alcohol group, linked via an oxygen atom.

134. (Previously Presented) A pharmaceutical formulation according to claim 133, wherein Q comprises a group selected from: ethanediol (glycol), propanediol, butanediol, glycerol, and erythritol.

Claim 135. (Canceled)

136. (Previously Presented) A pharmaceutical formulation according to claim 92, wherein the pharmaceutical formulation is a liposomal pharmaceutical formulation.

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137. (Previously Presented) A liposomal pharmaceutical formulation according to claim 136, wherein the liposomes of the liposomal pharmaceutical formulation are prepared using a mixture of lipids comprising, at least, vesicle-forming lipids and said short-chain sphingolipid.

138. (Previously Presented) A liposomal pharmaceutical formulation according to claim 137, wherein said mixture of lipids comprises phospholipids and said short-chain sphingolipid.

139. (Previously Presented) A liposomal pharmaceutical formulation according to claim 137, wherein said mixture of lipids comprises phospholipids, cholesterol, and said short-chain sphingolipid.

140. (Previously Presented) A liposomal pharmaceutical formulation according to claim 137, wherein said mixture of lipids comprises phosphatidylcholines, cholesterol, and said short-chain sphingolipid.

141. (Previously Presented) A liposomal pharmaceutical formulation according to claim 137, wherein said mixture of lipids comprises fully hydrogenated soy phosphatidylcholine (HSPC), cholesterol, and said short-chain sphingolipid.

142. (Previously Presented) A liposomal pharmaceutical formulation according to claim 137, wherein said mixture of lipids comprises dipalmitoyl-phosphatidylcholine (DPPC), cholesterol, and said short-chain sphingolipid.

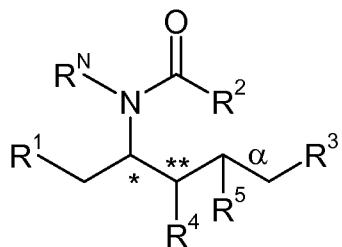
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143. (Previously Presented) A liposomal pharmaceutical formulation according to claim 137, wherein said mixture of lipids additionally comprises a vesicle-forming lipid which is derivatized with a polymer chain.

144. (Previously Presented) A liposomal pharmaceutical formulation according to claim 137, wherein said mixture of lipids additionally comprises a phosphatidylethanolamine (PE) which is derivatized with polyethyleneglycol (PEG).

145. (Previously Presented) A liposomal pharmaceutical formulation according to claim 137, wherein said mixture of lipids additionally comprises N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG2000-DSPE).

146. (Currently Amended) A pharmaceutical formulation according to claim 92, in the form of Caelyx® or Doxil® liposomes post-inserted with a short-chain sphingolipid selected from compounds of the following formula:



wherein:

R¹ is independently:

an O-linked saccharide group; or

an O-linked polyhydric alcohol group;

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or:

R^1 is independently:

an O-linked (optionally N-(C_{1-4} alkyl)-substituted amino)- C_{1-6} alkyl-phosphate group; or

an O-linked (polyhydric alcohol-substituted)- C_{1-6} alkyl-phosphate group;

R^2 is independently C_{3-9} alkyl,

and is independently unsubstituted or substituted;

R^3 is independently C_{7-19} alkyl,

and is independently unsubstituted or substituted;

R^4 is independently -H, -OH, or -O- C_{1-4} alkyl;

R^N is independently -H or C_{1-4} alkyl;

the bond marked with an alpha (α) is independently a single bond

or a double bond;

if the bond marked with an alpha (α) is a double bond, then R^5 is -H;

if the bond marked with an alpha (α) is a single bond, then R^5 is -H or -OH;

the carbon atom marked (*) is independently in an R-configuration or an

S-configuration;

the carbon atom marked (**) is independently in an R-configuration or an

S-configuration;

with the proviso that when R^1 is an O-linked saccharide group which is derived from galactopyranose, then R^1 is D-galactopyranosyl- β 1-;

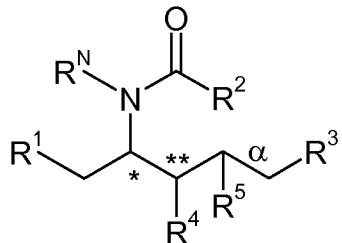
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and pharmaceutically acceptable salts thereof.

Claims 147-151. (Canceled)

152. (new) A pharmaceutical formulation suitable for parenteral administration comprising:

- (i) a drug; and
- (ii) a short-chain sphingolipid selected from compounds of the following formula:



wherein:

R¹ is independently an O-linked polyhydric alcohol group;

R² is independently C₃₋₉alkyl,

and is independently unsubstituted or substituted;

R³ is independently C₇₋₁₉alkyl,

and is independently unsubstituted or substituted;

R⁴ is independently -H, -OH, or -O-C₁₋₄alkyl;

R^N is independently -H or C₁₋₄alkyl;

the bond marked with an alpha (α) is a single bond;

R⁵ is -H or -OH;

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the carbon atom marked (*) is independently in an R-configuration or an S-configuration;

the carbon atom marked (**) is independently in an R-configuration or an S-configuration;

and pharmaceutically acceptable salts thereof.

153. (new) A pharmaceutical formulation suitable for parenteral administration comprising:

- (i) an amphiphilic drug; and
- (ii) a short-chain sphingolipid having the following formula ("3-O-methyl-C₈-SM"):

